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* * * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

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=> s disperant and solubilizing agent and antioxidant and ester
L1             0 DISPERANT AND SOLUBILIZING AGENT AND ANTIOXIDANT AND ESTER

=> s dispersant and solubilizing agent and antioxidant and ester
L2           489 DISPERSANT AND SOLUBILIZING AGENT AND ANTIOXIDANT AND ESTER

=> s beta sitosterol
L3         14665 BETA SITOSTEROL

=> s l2 and l3
L4            23 L2 AND L3

=>  s calcium hydroxide and calcium oxide and calcium salt and carboxylic acid
L5           507 CALCIUM HYDROXIDE AND CALCIUM OXIDE AND CALCIUM SALT AND CARBOXY
                 LIC ACID

=> s l4 and l5
L6            3 L4 AND L5

=> s sunflower oil
L7         25295 SUNFLOWER OIL

=> s l6 and l7
L8            3 L6 AND L7

=> s vegetable oil
L9         88770 VEGETABLE OIL

=> s l8 and l9
L10           3 L8 AND L9

=>  s tocopherol
L11        97971 TOCOPHEROL

=> s l10 and l11
L12           3 L10 AND L11

=> s alkyl polyglycoside
L13         4555 ALKYL POLYGLYCOSIDE

=> s l12 and l13
L14           3 L12 AND L13

=> d his

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     FILE 'CAPLUS, MEDLINE, USPATFULL, EMBASE' ENTERED AT 13:01:54 ON 25 OCT
     2006
L1             0 S DISPERANT AND SOLUBILIZING AGENT AND ANTIOXIDANT AND ESTER
L2           489 S DISPERSANT AND SOLUBILIZING AGENT AND ANTIOXIDANT AND ESTER
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L3         14665 S BETA SITOSTEROL
L4            23 S L2 AND L3
L5           507 S CALCIUM HYDROXIDE AND CALCIUM OXIDE AND CALCIUM SALT AND CARB
L6             3 S L4 AND L5
L7         25295 S SUNFLOWER OIL
L8             3 S L6 AND L7
L9         88770 S VEGETABLE OIL
L10            3 S L8 AND L9
L11        97971 S TOCOPHEROL
L12            3 S L10 AND L11
L13         4555 S ALKYL POLYGLYCOSIDE
L14            3 S L12 AND L13

=> d l14 1-3 ibib abs kwic

L14  ANSWER 1 OF 3  USPATFULL on STN
ACCESSION NUMBER:        2004:139409  USPATFULL
TITLE:                   Food additive compositions containing sterol
                         esters, solubilizing agents
                         , dispersants and antioxidants
INVENTOR(S):             Milstein, Norman, Montgomery, OH, UNITED STATES
                         Biermann, Manfred, Cincinnati, OH, UNITED STATES
                         Leidl, Peter, Illertissen, GERMANY, FEDERAL REPUBLIC OF
                         Von Kries, Rainer, Illertissen, GERMANY, FEDERAL
                         REPUBLIC OF

                              NUMBER         KIND    DATE
                         ---------------- ------ --------
PATENT INFORMATION:      US 2004106585      A1   20040603
APPLICATION INFO.:       US 2003-702316     A1   20031105  (10)
RELATED APPLN. INFO.:    Division of Ser. No. US 2002-126284, filed on 19 Apr
                         2002, GRANTED, Pat. No. US 6713466 Division of Ser. No.
                         US 1998-83584, filed on 21 May 1998, GRANTED, Pat. No.
                         US 6394230 Continuation-in-part of Ser. No. US
                         1998-72434, filed on 4 May 1998, ABANDONED

                               NUMBER         DATE
                         ------------------ --------
PRIORITY INFORMATION:    US 1997-69790P     19971216 (60)
DOCUMENT TYPE:           Utility
FILE SEGMENT:            APPLICATION
LEGAL REPRESENTATIVE:    COGNIS CORPORATION, PATENT DEPARTMENT, 300 BROOKSIDE
                         AVENUE, AMBLER, PA, 19002
NUMBER OF CLAIMS:        92
EXEMPLARY CLAIM:         1
LINE COUNT:              781
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB       A food additive useful for lowering serum cholesterol in humans contains
         a sterol or stanol ester of a fatty acid or a dicarboxylic
         acid ester of a sterol or stanol made by reacting a sterol,
         stanol and a carboxylic acid in the presence of an
         effective amount of a catalyst selected from the group consisting of
         calcium oxide, calcium hydroxide,
         a calcium salt of a carboxylic
         acid, magnesium hydroxide and combinations thereof described
         herein below.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI       Food additive compositions containing sterol esters,
         solubilizing agents, dispersants and
         antioxidants
AB       A food additive useful for lowering serum cholesterol in humans contains
         a sterol or stanol ester of a fatty acid or a dicarboxylic
         acid ester of a sterol or stanol made by reacting a sterol,
```

Applicant

stanol and a carboxylic acid in the presence of an effective amount of a catalyst selected from the group consisting of calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide and combinations thereof described herein below.

SUMM . . . relationship to cholesterol but differ in the configuration of the side chains at the 17-position. It is well known that .beta .-sitosterol and the fatty acid esters of . beta.-sitosterol are effective in reducing serum cholesterol. Recent studies have found that β-sitostanol and the fatty acid esters of β-sitostanol are particularly effective in reducing serum cholesterol and LDL levels. It has been recently reported that the fatty acid esters of β-sitostanol are particularly effective cholesterol-reducing agents presumably because they are in solution. Such esters can be introduced into the body as additives in food products such as margarine. Margarines containing .beta.-sitosterol and those containing .beta.-sitosterol fatty acid esters as well as margarines containing β-sitostanol and β-sitostanol fatty acid esters have been shown to reduce serum cholesterol levels in humans.

SUMM [0004] The present invention pertains to a food additive containing a sterol or stanol ester of a fatty acid or a dicarboxylic acid ester of a sterol or stanol made by the process described herein below. The food additive can be incorporated into food. . . absorption of cholesterol from foods and/or beverages. The food additive is prepared by combining a sterol and/or stanol fatty acid ester thereof and/or a dicarboxylic acid ester of a sterol or stanol made by the process described herein and an edible solubilizing agent, an effective amount of a suitable antioxidant and an effective amount of a suitable dispersant. The sterol and/or stanol esters made by the process described herein can be used without removing the catalyst because the catalyst is non-toxic and used at low levels. Another advantage is that when the fatty acid esters of sterols or stanols are prepared by transesterification, the ester that is transesterified can be either a lower alkyl ester such as a methyl or an ethyl ester or a triglyceride which is a triglyceryl ester of a C.sub.6-22 fatty acid such as a conventional fat or oil.

SUMM . . . cholesterol into the bloodstream which comprises orally introducing into the body an effective amount of a substance containing a β-sitostanol ester made by reacting a stanol and a carboxylic acid in the presence of an effective amount of a catalyst selected from the group consisting of calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide and combinations thereof.

DRWD [0009] The food additive according to the invention is comprised of a sterol and/or stanol ester of a fatty acid wherein the ester is made by reacting a sterol and/or stanol with a fatty acid having from 6 to 22 carbon atoms in the presence of an effective amount of a catalyst selected from the group consisting of calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide and combinations thereof or a dicarboxylic acid ester of a sterol or stanol of the formula I. Since the catalyst is non-toxic and used at low levels, the sterol and/or stanol ester of the fatty acid can be added directly to foods without further processing such as removal of the catalyst. The. . . suitable sterols include, but are not limited to, campesterol, ergosterol, stigmasterol, sitosterol or a combination thereof. A preferred sterol is .beta.-sitosterol. A commercially available combination of sterols is GENEROL® 122N

sterols as set forth herein. The stanol can be any stanol.. . .

DRWD [0010] The amount of sterol and/or stanol fatty acid ester that can be used in the food additive is an effective amount which is any amount necessary to either reduce. . . from foods and/or beverages. A preferred food additive composition of the instant invention comprises from about 70% to about 80% vegetable oil, from about 1% to about 2% tocopherols, and from about 10% to about 25% sterol and/or stanol fatty acid ester prepared by the method according to the invention.

DRWD [0011] The food additive is prepared by combining a sterol and/or stanol ester of a fatty acid made by the process described herein and an edible solubilizing agent, an effective amount of a suitable antioxidant and an effective amount of a suitable dispersant. The solubilizing agent can be vegetable oil such as, for example, sunflower oil, palm kernel oil, coconut oil, rape seed oil, tallow, corn oil, canola oil, linseed oil, palm oil, olive oil, sesame oil, safflower oil, and the like, monoglycerides, diglycercides, triglycercides, tocopherols, and the like, and mixtures thereof. The antioxidant can be ascorbic acid (Vitamin C), tocopherols such as α- tocopherol (vitamin E), β-carotene, an extract of the bark of the maritime pine, Pinus maritima and combinations thereof. The extract of. . . precipitate which may be purified by repeating the dissolution in ethyl acetate and precipitation with chloroform. Mixtures of the above antioxidants can also be used.

DRWD [0012] A suitable dispersant is any biologically acceptable surface active agent, examples of which include, but are not limited to, an alkyl polyglycoside, lecithin, polysorbate 80, sodium lauryl sulfate, and the like. The alkyl polyglycosides which can be used in the invention have the formula V

DRWD . . . a value from 0 to about 12; a is a number having a value from 1 to about 6. Preferred alkyl polyglycosides which can be used in the compositions according to the invention have the formula I wherein Z is a glucose residue and b is zero. Such alkyl polyglycosides are commercially available, for example, as APG®, GLUCOPON®, PLANTAREN® or AGRIMUL® surfactants from Henkel Corporation, Ambler, Pa., 19002. Examples of. . .

DRWD [0014] 1. GLUCOPON® 220 Surfactant--an alkyl polyglycoside in which the alkyl group contains 8 to 10 carbon atoms and having an average degree of polymerization of 1.5.

DRWD [0015] 2. GLUCOPON®225 Surfactant--an alkyl polyglycoside in which the alkyl group contains 8 to 10 carbon atoms and having an average degree of polymerization of 1.7.

DRWD [0016] 3. GLUCOPON® 600 Surfactant--an alkyl polyglycoside in which the alkyl group contains 12 to 16 carbon atoms and having an average degree of polymerization of 1.4.

DRWD [0017] 4. GLUCOPON® 625 Surfactant--an alkyl polyglycoside in which the alkyl group contains 12 to 16 carbon atoms and having an average degree of polymerization of 1.4.

DRWD [0018] 5. APG® 325 Surfactant--an alkyl polyglycoside in which the alkyl group contains 9 to 11 carbon atoms and having an average degree of polymerization of 1.6.

DRWD [0019] 6. PLANTAREN® 2000 Surfactant--an alkyl polyglycoside in which the alkyl group contains 8 to 16 carbon atoms and having an average degree of polymerization of 1.4.

DRWD [0020] 7. PLANTAREN® 1300 Surfactant--an alkyl polyglycoside in which the alkyl group contains 12 to 16 carbon atoms and having an average degree of polymerization of 1.6.

DRWD [0021] 8. AGRIMUL® PG 2067 Surfactant--an alkyl polyglycoside in which the alkyl group contains 8 to 10 carbon atoms and having an average degree of polymerization of 1.7.

DRWD [0022] Other examples include alkyl polyglycoside

surfactant compositions which are comprised of mixtures of compounds of formula I as described in U.S. Pat. Nos. 5,266,690 and. . .

DRWD . . . . Products (1985), the entire contents of which are incorporated herein by reference. The amount of sterol and/or stanol fatty acid ester useful in the novel food additive is an effective amount which is any amount necessary to either reduce serum cholesterol. . . from foods and/or beverages. A preferred food additive composition of the instant invention comprises from about 70% to about 80% vegetable oil, from about 1% to about 2% tocopherols, and from about 10% to about 25% sterol and/or stanol fatty acid ester prepared by the method according to the invention. Particularly preferred compositions are composed of from about 70% to about 80% sunflower oil and/or rape seed oil, from about 1% to about 2% vitamin E and/or an extract of the bark of the maritime pine, Pinus maritima and from about 10% to about 25% of a sterol and/or stanol fatty acid ester prepared by the method according to the invention.

DRWD . . . cholesterol into the bloodstream which comprises orally introducing into the body an effective amount of a substance containing a β-sitostanol ester made by reacting β-sitostanol and a carboxylic acid in the presence of an effective amount of a catalyst selected from the group consisting of calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide and combinations thereof. The cholesterol-lowering ability of fatty acid esters of β-sitostanol is described in U.S. Pat. No. 5,502,045, the entire contents of which are incorporated herein by reference. The fatty acid esters of β-sitostanol made by the process described herein can be orally introduced by ingesting food products containing the food additives. . . cooking oils or shortening containing a food additive according to the invention. A particularly effective amount of β-sitostanol fatty acid esters is from about 0.2 to about 20 grams per day. Particularly preferred additives are composed of from about 70% to about 80% sunflower oil and/or rape seed oil, from about 1% to about 2% vitamin E and/or an extract of the bark of the maritime pine, Pinus maritima and from about 10% to about 25% of a β-sitostanol fatty acid ester prepared by the method according to the invention.

DRWD [0025] In regard to the esterification process used to make the sterol and/or stanol esters which can be used in the novel food additive, any aliphatic, cycloaliphatic, or aromatic mono- or poly-carboxylic acid having at least 2 carbon atoms or mixtures of such acids can be used in the process according to the invention. Examples of aliphatic mono-carboxylic acids include, but are not limited to acetic, propionic, valeric, pelargonic, palmitic, lauric, oleic, linoleic acid, and the like. Examples of cycloaliphatic mono-carboxylic acids include, but are not limited to cyclopentane carboxylic acid, cyclohexane carboxylic acid, cyclohexene carboxylic acid and the like. Examples of aromatic mono-carboxylic acids include, but are not limited to benzoic acid, toluic acid, aminobenzoic acid and the like. Examples of aliphatic poly-carboxylic acids include, but are not limited to oxalic, malonic, adipic, azelaic acid, C-36 dimer acid, citric acid and the like. Examples of aromatic poly-carboxylic acids include, but are not limited to phthalic acid, trimellitic acid and the like. Preferred carboxylic acids are mixtures of long chain carboxylic acids such as those derived from naturally occurring oils such as sunflower oil, palm kernel oil, coconut oil, rape seed oil, tallow, corn oil, canola oil, linseed oil, palm oil, olive oil, sesame. . . Fat Products, the entire contents of which are incorporated herein by reference. Preferred fatty acid mixtures are those obtained from

sunflower oil and rape seed oil.

DRWD [0026] The direct or transesterification modifications of the esterification processes can be carried out in the presence of a calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide catalyst or a combination of such catalysts. One advantage of the method according to the invention is that. . . removed by contacting the reaction product with a chelating agent such as L-tartaric acid or EDTA. The preferred catalysts are calcium hydroxide, calcium oxide and the calcium salt of a fatty acid having from about 10 to about 22 carbon atoms. Calcium oxide is a particularly preferred catalyst. The amount that can be used is an effective amount which is any amount required to effect the conversion of a sterol or stanol to the corresponding ester. Typically, the amount will range from about 0.01% to 0.2% based on the total weight of the reaction mixture and. . .

DRWD [0028] The transesterification process according to the invention can be carried out using any type of carboxylic acid ester. Such esters include simple esters such as lower alkyl esters which include, for example, methyl, ethyl, propyl, or butyl esters or higher alkyl esters such as pentyl, hexyl, heptyl and the like or triglycerides which are triglyceryl esters of C.sub.6-22 fatty acids such as conventional fats or oils. The transesterification conditions will vary according to the type of ester employed. If a glyceride is used, the temperature will be in the range of from about 210° C. to about 250° C., preferably from about 220° C. to about 230° C. If an ester of a lower molecular weight alcohol is used such as a methyl or ethyl ester such that the alcohol formed will be readily removed under the reaction conditions as, opposed to the use of a. . .

DRWD . . . commercial scale is that since no low molecular weight alcohol is produced as in, for example, transesterification of a methyl ester, there is no foaming in a reactor due to the evolution of the low molecular weight alcohol such as methanol.. . .

DRWD [0030] The process according to the invention is particularly useful for the preparation of dicarboxylic acid esters of sterols and/or stanols wherein the dicarboxylic acids are fully esterified or partially esterified. Such compounds have the formula I. . .

DRWD . . . be hydrogen. In the instances where only one of R.sup.2 or R.sup.3 is hydrogen refer to the partial or half esters of the dicarboxylic acids. These compounds are useful as for reducing serum cholesterol and LDL levels. Preferred compounds of the. . .

DRWD [0033] Most preferred compounds of the formula I include the disitostanol ester of azelaic acid, the disitostanol ester of brassylic acid, the disitostanol ester of decanedioic acid, the disitostanol ester of dodecanedioic acid, the disitosterol ester of azelaic acid, the disitosterol ester of brassylic acid, the disitostanol ester of decanedioic acid and, the disitosterol ester of dodecanedioic acid, the sitostanol monoester of azelaic acid, the sitostanol monoester of brassylic acid, the sitostanol monoester of decanedioic. . .

DETD . . . agitating with a nitrogen sparge. This required about one half hour. After the addition of the stanol, 0.34 grams of calcium hydroxide was added and the pressure was gradually decreased to 27 inches, while the temperature was increased to 230° C. After. . .

DETD . . . agitating with a nitrogen sparge. This required about one half hour. After the addition of the stanol, 0.34 grams of calcium oxide was added and the pressure was gradually decreased to 27 inches, while the temperature was increased to 210° C. After. .

DETD [0043] A dicarboxylic ester is made by reacting one mole of a

sterol or stanol with a 1/2 mole of a dicarboxylic acid in the presence of calcium oxide at 210 degrees under reduced pressure according to the procedure of Examples 1 and 2 above.

DETD . . . with a nitrogen sparge. This required about one half hour. After the addition of the GENEROL® 122N, 0.34 grams of calcium oxide was added and the pressure was gradually decreased to 30 mbar while the temperature was increased to 210° C. After. . .

CLM What is claimed is:

1. A process for making a food additive comprising combining an edible solubilizing agent, an effective amount of a suitable antioxidant, an effective amount of a suitable dispersant and a sterol or stanol ester made by reacting a sterol or a stanol and a carboxylic acid in the presence of an effective amount of a catalyst selected from the group consisting of calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide and combinations thereof.

2. The process of claim 1 wherein the sterol is .beta.-sitosterol.

4. The process of claim 1 wherein the catalyst is calcium hydroxide, calcium oxide or a calcium salt of a carboxylic acid.

5. The process of claim 1 wherein the carboxylic acid is a carboxylic acid having from about 2 to 22 carbon atoms.

6. A process which comprises reacting β-sitostanol with a carboxylic acid in the presence of an effective amount of calcium oxide.

7. The process of claim 6 wherein the carboxylic acid is a carboxylic acid having from about 2 to 22 carbon atoms.

8. The process of claim 1 wherein the carboxylic acid is a mixture of long chain carboxylic acids derived from sunflower oil, palm kernel oil, coconut oil, rape seed oil, tallow, corn oil, canola oil, linseed oil, palm oil, olive oil, sesame. . .

9. A process which comprises reacting .beta.-sitosterol with a carboxylic acid in the presence of an effective amount of calcium oxide.

10. The process of claim 1 wherein the antioxidant is vitamin C, vitamin E, β-carotene, an extract of the bark of the maritime pine, Pinus maritima, or combinations thereof.

. . .

11. A food additive composition comprising an edible solubilizing agent, an effective amount of a suitable antioxidant and an effective amount of a suitable dispersant and a sterol or stanol ester made by reacting a sterol or a stanol and a carboxylic acid in the presence of an effective amount of a catalyst selected from the group consisting of calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide and combinations thereof.

12. The composition of claim 11 wherein the sterol is .beta.-

sitosterol.

14. The composition of claim 11 wherein the catalyst is calcium hydroxide, calcium oxide or a calcium salt of a carboxylic acid.

15. The composition of claim 11 wherein the carboxylic acid is a carboxylic acid having from about 2 to 22 carbon atoms.

16. The composition of claim 11 wherein the antioxidant is vitamin C, vitamin E, β-carotene, an extract of the bark of the maritime pine, Pinus maritima, or combinations thereof.

. . .

17. The composition of claim 11 wherein the carboxylic acid is a mixture of long chain carboxylic acids derived from sunflower oil, palm kernel oil, coconut oil, rape seed oil, tallow, corn oil, canola oil, linseed oil, palm oil, olive oil, sesame. . .

18. The composition of claim 17 wherein the mixture of long chain carboxylic acids derived from sunflower oil.

19. A process which comprises reacting .beta.-sitosterol with a carboxylic acid in the presence of an effective amount of calcium oxide.

20. The composition of claim 11 wherein the antioxidant is vitamin C, vitamin E, β-carotene, an extract of the bark of the maritime pine, Pinus maritima, or combinations thereof.

. . .

21. A food additive made by the process comprising combining an edible solubilizing agent, an effective amount of a suitable antioxidant, an effective amount of a suitable dispersant and a sterol or stanol ester made by reacting a sterol or a stanol and a carboxylic acid in the presence of an effective amount of a catalyst selected from the group consisting of calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide and combinations thereof.

22. The food additive of claim 21 wherein the sterol is .beta.-sitosterol.

24. The food additive of claim 21 wherein the catalyst is calcium hydroxide, calcium oxide or a calcium salt of a carboxylic acid.

25. The food additive of claim 21 wherein the carboxylic acid is a carboxylic acid having from about 2 to 22 carbon atoms.

26. The food additive of claim 21 wherein the carboxylic acid is a mixture of long chain carboxylic acids derived from sunflower oil, palm kernel oil, coconut oil, rape seed oil, tallow, corn oil, canola oil, linseed oil, palm oil, olive oil, sesame. . .

27. The food additive of claim 21 wherein the antioxidant is vitamin C, vitamin E, β-carotene, an extract of the bark of the maritime pine, Pinus maritima, or combinations thereof.

. . .

28. A composition comprising an edible solubilizing

agent, an effective amount of a suitable antioxidant, an effective amount of a suitable dispersant and a compound of the formula I ##STR4## wherein R.sup.1 is an aliphatic or aromatic moiety having from one to. . .

38. A composition made by the process which comprises combining an edible solubilizing agent, an effective amount of a suitable antioxidant, an effective amount of a suitable dispersant and a compound of the formula I ##STR10## wherein R.sup.1 is an aliphatic or aromatic moiety having from one to. . . . of cholesterol into the bloodstream comprising orally introducing into the body an effective amount of a substance containing a β-sitostanol ester wherein the ester is made by reacting β-sitostanol and a carboxylic acid in the presence of an effective amount of a catalyst selected from the group consisting of calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide and combinations thereof.

49. The method of claim 48 wherein the substance containing a β-sitostanol ester is comprised of an additive comprised of from about 70% to about 80% sunflower oil, rape seed oil or a combination thereof; from about 1% to about 2% vitamin E, an extract of the bark. . . maritime pine, Pinus maritima or a combination thereof; and from about 10% to about 25% of a β-sitostanol fatty acid ester prepared by the method according to the invention.

51. The process of claim 48 wherein the catalyst is calcium hydroxide, calcium oxide or a calcium salt of a carboxylic acid.

52. The process of claim 48 wherein the carboxylic acid is a carboxylic acid having from about 2 to 22 carbon atoms.

53. A process which comprises reacting a sterol, a stanol, or a combination thereof with a carboxylic acid in the presence of an effective amount of a catalyst selected from the group consisting of calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide and combinations thereof.

54. The process of claim 53 wherein said sterol is .beta.-sitosterol.

56. The process of claim 53 wherein said catalyst is calcium hydroxide, calcium oxide or a calcium salt of a carboxylic acid.

57. The process of claim 53 wherein said carboxylic acid is a carboxylic acid having from about 2 to 22 carbon atoms.

58. A process which comprises reacting β-sitostanol with a carboxylic acid in the presence of an effective amount of calcium oxide.

59. The process of claim 58 wherein said carboxylic acid is a carboxylic acid having from about 2 to 22 carbon atoms.

60. The process of claim 59 wherein said carboxylic

acid is a mixture of long chain carboxylic acids derived from sunflower oil, palm kernel oil, coconut oil, rape seed oil, tallow, corn oil, canola oil, linseed oil, palm oil, olive oil, sesame. . .

. . . the steps of: (1) forming a reaction mixture comprised of a sterol, a stanol, or a combination thereof with a carboxylic acid in the presence of an effective amount of a catalyst selected from the group consisting of calcium hydroxide, magnesium hydroxide and a combination in a reaction zone; (2) passing at least a portion of said reaction mixture through. . .

63. The process of claim 61 wherein said catalyst is calcium oxide.

64. A process which comprises reacting a sterol, a stanol, or a combination thereof with an carboxylic acid ester in the presence of an effective amount of a catalyst selected from the group consisting of calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide and combinations thereof.

65. The process of claim 64 wherein said sterol is .beta.-sitosterol.

67. The process of claim 64 wherein said catalyst is calcium hydroxide, calcium oxide or a calcium salt of a carboxylic acid.

68. The process of claim 64 wherein said carboxylic acid is a carboxylic acid having from about 2 to 22 carbon atoms.

69. The process of claim 64 wherein said ester is a methyl ester of a C.sub.6-22 fatty acid or a triglyceride.

70. A process which comprises reacting P-sitostanol with a carboxylic acid ester in the presence of an effective amount of calcium oxide.

71. A process which comprises the steps of: (1) forming a reaction mixture comprised of a sterol, a stanol, or a combination thereof with a carboxylic acid ester in the presence of an effective amount of a catalyst selected from the group consisting of calcium hydroxide, magnesium hydroxide and a combination in a reaction zone; (2) passing at least a portion of said reaction mixture through. . .

. . . with a dicarboxylic acid in the presence of an effective amount of a catalyst selected from the group consisting of calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide and combinations thereof.

92. The compound of claim 83 wherein said catalyst is calcium oxide.

L14 ANSWER 2 OF 3 USPATFULL on STN
ACCESSION NUMBER: 2002:242810 USPATFULL
TITLE: Processes for preparing sterol esters
INVENTOR(S): Milstein, Norman, Montgomery, OH, UNITED STATES
Biermann, Manfred, Cincinnati, OH, UNITED STATES
Leidl, Peter, lllertissen, GERMANY, FEDERAL REPUBLIC OF
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REPUBLIC OF

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002131991	A1	20020919
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APPLICATION INFO.:	US 2002-126284	A1	20020419 (10)

RELATED APPLN. INFO.: Division of Ser. No. US 1998-83584, filed on 21 May 1998, GRANTED, Pat. No. US 6394230 Continuation-in-part of Ser. No. US 1998-72434, filed on 4 May 1998, ABANDONED

	NUMBER	DATE
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DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: COGNIS CORPORATION, 2500 RENAISSANCE BLVD., SUITE 200, GULPH MILLS, PA, 19406
NUMBER OF CLAIMS: 92
EXEMPLARY CLAIM: 1
LINE COUNT: 781
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A food additive useful for lowering serum cholesterol in humans contains a sterol or stanol ester of a fatty acid or a dicarboxylic acid ester of a sterol or stanol made by reacting a sterol, stanol and a carboxylic acid in the presence of an effective amount of a catalyst selected from the group consisting of calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide and combinations thereof described herein below.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Processes for preparing sterol esters

AB A food additive useful for lowering serum cholesterol in humans contains a sterol or stanol ester of a fatty acid or a dicarboxylic acid ester of a sterol or stanol made by reacting a sterol, stanol and a carboxylic acid in the presence of an effective amount of a catalyst selected from the group consisting of calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide and combinations thereof described herein below.

SUMM . . . relationship to cholesterol but differ in the configuration of the side chains at the 17-position. It is well known that .beta.-sitosterol and the fatty acid esters of .beta.-sitosterol are effective in reducing serum cholesterol. Recent studies have found that β-sitostanol and the fatty acid esters of β-sitostanol are particularly effective in reducing serum cholesterol and LDL levels. It has been recently reported that the fatty acid esters of β-sitostanol are particularly effective cholesterol-reducing agents presumably because they are in solution. Such esters can be introduced into the body as additives in food products such as margarine. Margarines containing .beta.-sitosterol and those containing .beta.-sitosterol fatty acid esters as well as margarines containing β-sitostanol and β-sitostanol fatty acid esters have been shown to reduce serum cholesterol levels in humans.

SUMM [0004] The present invention pertains to a food additive containing a sterol or stanol ester of a fatty acid or a dicarboxylic acid ester of a sterol or stanol made by the process described herein below. The food additive can be incorporated into food. . .

absorption of cholesterol from foods and/or beverages. The food additive is prepared by combining a sterol and/or stanol fatty acid ester thereof and/or a dicarboxylic acid ester of a sterol or stanol made by the process described herein and an edible solubilizing agent, an effective amount of a suitable antioxidant and an effective amount of a suitable dispersant. The sterol and/or stanol esters made by the process described herein can be used without removing the catalyst because the catalyst is non-toxic and used at low levels. Another advantage is that when the fatty acid esters of sterols or stanols are prepared by transesterification, the ester that is transesterified can be either a lower alkyl ester such as a methyl or an ethyl ester or a triglyceride which is a triglyceryl ester of a C.sub.6-22 fatty acid such as a conventional fat or oil.

SUMM . . . cholesterol into the bloodstream which comprises orally introducing into the body an effective amount of a substance containing a β-sitostanol ester made by reacting a stanol and a carboxylic acid in the presence of an effective amount of a catalyst selected from the group consisting of calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide and combinations thereof.

SUMM [0009] The food additive according to the invention is comprised of a sterol and/or stanol ester of a fatty acid wherein the ester is made by reacting a sterol and/or stanol with a fatty acid having from 6 to 22 carbon atoms in the presence of an effective amount of a catalyst selected from the group consisting of calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide and combinations thereof or a dicarboxylic acid ester of a sterol or stanol of the formula I. Since the catalyst is non-toxic and used at low levels, the sterol and/or stanol ester of the fatty acid can be added directly to foods without further processing such as removal of the catalyst. The. . . suitable sterols include, but are not limited to, campesterol, ergosterol, stigmasterol, sitosterol or a combination thereof. A preferred sterol is .beta.-sitosterol. A commercially available combination of sterols is GENEROL® 122N sterols as set forth herein. The stanol can be any stanol.. . .

SUMM [0010] The amount of sterol and/or stanol fatty acid ester that can be used in the food additive is an effective amount which is any amount necessary to either reduce. . . from foods and/or beverages. A preferred food additive composition of the instant invention comprises from about 70% to about 80% vegetable oil, from about 1% to about 2% tocopherols, and from about 10% to about 25% sterol and/or stanol fatty acid ester prepared by the method according to the invention.

SUMM [0011] The food additive is prepared by combining a sterol and/or stanol ester of a fatty acid made by the process described herein and an edible solubilizing agent, an effective amount of a suitable antioxidant and an effective amount of a suitable dispersant. The solubilizing agent can be vegetable oil such as, for example, sunflower oil, palm kernel oil, coconut oil, rape seed oil, tallow, corn oil, canola oil, linseed oil, palm oil, olive oil, sesame oil, safflower oil, and the like, monoglycerides, diglycerides, triglycercides, tocopherols, and the like, and mixtures thereof. The antioxidant can be ascorbic acid (Vitamin C), tocopherols such as α- tocopherol (vitamin E), β-carotene, an extract of the bark of the maritime pine, Pinus maritima and combinations thereof. The extract of. . . precipitate which may be purified by repeating the dissolution in ethyl acetate and precipitation with chloroform. Mixtures of the above antioxidants can also be used.

SUMM [0012] A suitable dispersant is any biologically acceptable surface active agent, examples of which include, but are not limited to, an alkyl polyglycoside, lecithin, polysorbate 80, sodium lauryl sulfate, and the like. The alkyl polyglycosides which can be used in the invention have the formula V

SUMM . . . a value from 0 to about 12; a is a number having a value from 1 to about 6. Preferred alkyl polyglycosides which can be used in the compositions according to the invention have the formula I wherein Z is a glucose residue and b is zero. Such alkyl polyglycosides are commercially available, for example, as APG®, GLUCOPON®, PLANTAREN® or AGRIMUL® surfactants from Henkel Corporation, Ambler, Pa., 19002. Examples of. . .

SUMM [0014] 1. GLUCOPON® 220 Surfactant--an alkyl polyglycoside in which the alkyl group contains 8 to 10 carbon atoms and having an average degree of polymerization of 1.5.

SUMM [0015] 2. GLUCOPON® 225 Surfactant--an alkyl polyglycoside in which the alkyl group contains 8 to 10 carbon atoms and having an average degree of polymerization of 1.7.

SUMM [0016] 3. GLUCOPON® 600 Surfactant--an alkyl polyglycoside in which the alkyl group contains 12 to 16 carbon atoms and having an average degree of polymerization of 1.4.

SUMM [0017] 4. GLUCOPON® 625 Surfactant--an alkyl polyglycoside in which the alkyl group contains 12 to 16 carbon atoms and having an average degree of polymerization of 1.4.

SUMM [0018] 5. APG® 325 Surfactant--an alkyl polyglycoside in which the alkyl group contains 9 to 11 carbon atoms and having an average degree of polymerization of 1.6.

SUMM [0019] 6. PLANTAREN® 2000 Surfactant--an alkyl polyglycoside in which the alkyl group contains 8 to 16 carbon atoms and having an average degree of polymerization of 1.4.

SUMM [0020] 7. PLANTAREN® 1300 Surfactant--an alkyl polyglycoside in which the alkyl group contains 12 to 16 carbon atoms and having an average degree of polymerization of 1.6.

SUMM [0021] 8. AGRIMUL® PG 2067 Surfactant--an alkyl polyglycoside in which the alkyl group contains 8 to 10 carbon atoms and having an average degree of polymerization of 1.7.

SUMM [0022] Other examples include alkyl polyglycoside surfactant compositions which are comprised of mixtures of compounds of formula I as described in U.S. Pat. No. 5,266,690 and. . .

SUMM . . . Products (1985), the entire contents of which are incorporated herein by reference. The amount of sterol and/or stanol fatty acid ester useful in the novel food additive is an effective amount which is any amount necessary to either reduce serum cholesterol. . . from foods and/or beverages. A preferred food additive composition of the instant invention comprises from about 70% to about 80% vegetable oil, from about 1% to about 2% tocopherols, and from about 10% to about 25% sterol and/or stanol fatty acid ester prepared by the method according to the invention. Particularly preferred compositions are composed of from about 70% to about 80% sunflower oil and/or rape seed oil, from about 1% to about 2% vitamin E and/or an extract of the bark of the maritime pine, Pinus maritima and from about 10% to about 25% of a sterol and/or stanol fatty acid ester prepared by the method according to the invention.

SUMM . . . cholesterol into the bloodstream which comprises orally introducing into the body an effective amount of a substance containing a β-sitostanol ester made by reacting β-sitostanol and a carboxylic acid in the presence of an effective amount of a catalyst selected from the group consisting of calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide and combinations thereof. The cholesterol-lowering ability of fatty acid esters of

β-sitostanol is described in U.S. Pat. No. 5,502,045, the entire contents of which are incorporated herein by reference. The fatty acid esters of β-sitostanol made by the process described herein can be orally introduced by ingesting food products containing the food additives. . . . cooking oils or shortening containing a food additive according to the invention. A particularly effective amount of β-sitostanol fatty acid esters is from about 0.2 to about 20 grams per day. Particularly preferred additives are composed of from about 70% to about 80% sunflower oil and/or rape seed oil, from about 1% to about 2% vitamin E and/or an extract of the bark of the maritime pine, Pinus maritima and from about 10% to about 25% of a β-sitostanol fatty acid ester prepared by the method according to the invention.

SUMM [0025] In regard to the esterification process used to make the sterol and/or stanol esters which can be used in the novel food additive, any aliphatic, cycloaliphatic, or aromatic mono- or poly-carboxylic acid having at least 2 carbon atoms or mixtures of such acids can be used in the process according to the invention. Examples of aliphatic mono-carboxylic acids include, but are not limited to acetic, propionic, valeric, pelargonic, palmitic, lauric, oleic, linoleic acid, and the like. Examples of cycloaliphatic mono-carboxylic acids include, but are not limited to cyclopentane carboxylic acid, cyclohexane carboxylic acid, cyclohexene carboxylic acid and the like. Examples of aromatic mono-carboxylic acids include, but are not limited to benzoic acid, toluic acid, aminobenzoic acid and the like. Examples of aliphatic poly-carboxylic acids include, but are not limited to oxalic, malonic, adipic, azelaic acid, C-36 dimer acid, citric acid and the like. Examples of aromatic poly-carboxylic acids include, but are not limited to phthalic acid, trimellitic acid and the like. Preferred carboxylic acids are mixtures of long chain carboxylic acids such as those derived from naturally occurring oils such as sunflower oil, palm kernel oil, coconut oil, rape seed oil, tallow, corn oil, canola oil, linseed oil, palm oil, olive oil, sesame. . . . Fat Products, the entire contents of which are incorporated herein by reference. Preferred fatty acid mixtures are those obtained from sunflower oil and rape seed oil.

SUMM [0026] The direct or transesterification modifications of the esterification processes can be carried out in the presence of a calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide catalyst or a combination of such catalysts. One advantage of the method according to the invention is that. . . removed by contacting the reaction product with a chelating agent such as L-tartaric acid or EDTA. The preferred catalysts are calcium hydroxide, calcium oxide and the calcium salt of a fatty acid having from about 10 to about 22 carbon atoms. Calcium oxide is a particularly preferred catalyst. The amount that can be used is an effective amount which is any amount required to effect the conversion of a sterol or stanol to the corresponding ester. Typically, the amount will range from about 0.01% to 0.2% based on the total weight of the reaction mixture and. . .

SUMM [0028] The transesterification process according to the invention can be carried out using any type of carboxylic acid ester. Such esters include simple esters such as lower alkyl esters which include, for example, methyl, ethyl, propyl, or butyl esters or higher alkyl esters such as pentyl, hexyl, heptyl and the like or triglycerides which are triglyceryl esters of C.sub.6-22 fatty acids such as conventional fats or oils. The transesterification conditions will vary according to the type of ester employed. If a glyceride is

used, the temperature will be in the range of from about 210° C. to about 250° C., preferably from about 220° C. to about 230° C. If an ester of a lower molecular weight alcohol is used such as a methyl or ethyl ester such that the alcohol formed will be readily removed under the reaction conditions as, opposed to the use of a. . .

SUMM . . . commercial scale is that since no low molecular weight alcohol is produced as in, for example, transesterification of a methyl ester, there is no foaming in a reactor due to the evolution of the low molecular weight alcohol such as methanol.. . .

SUMM [0030] The process according to the invention is particularly useful for the preparation of dicarboxylic acid esters of sterols and/or stanols wherein the dicarboxylic acids are fully esterified or partially esterified. Such compounds have the formula I. . .

SUMM . . . be hydrogen. In the instances where only one of R.sup.2 or R.sup.3 is hydrogen refer to the partial or half esters of the dicarboxylic acids. These compounds are useful as for reducing serum cholesterol and LDL levels. Preferred compounds of the. . .

SUMM [0033] Most preferred compounds of the formula I include the disitostanol ester of azelaic acid, the disitostanol ester of brassylic acid, the disitostanol ester of decanedioic acid, the disitostanol ester of dodecanedioic acid, the disitosterol ester of azelaic acid, the disitosterol ester of brassylic acid, the disitostanol ester of decanedioic acid and, the disitosterol ester of dodecanedioic acid, the sitostanol monoester of azelaic acid, the sitostanol monoester of brassylic acid, the sitostanol monoester of decanedioic. . .

DETD . . . agitating with a nitrogen sparge. This required about one half hour. After the addition of the stanol, 0.34 grams of calcium hydroxide was added and the pressure was gradually decreased to 27 inches, while the temperature was increased to 230° C. After. . .

DETD . . . agitating with a nitrogen sparge. This required about one half hour. After the addition of the stanol, 0.34 grams of calcium oxide was added and the pressure was gradually decreased to 27 inches, while the temperature was increased to 210° C. After. .

DETD [0043] A dicarboxylic ester is made by reacting one mole of a sterol or stanol with a 1/2 mole of a dicarboxylic acid in the presence of calcium oxide at 210 degrees under reduced pressure according to the procedure of Examples 1 and 2 above.

DETD . . . with a nitrogen sparge. This required about one half hour. After the addition of the GENEROL® 122N, 0.34 grams of calcium oxide was added and the pressure was gradually decreased to 30 mbar while the temperature was increased to 210° C. After. . .

CLM What is claimed is:

1. A process for making a food additive comprising combining an edible solubilizing agent, an effective amount of a suitable antioxidant, an effective amount of a suitable dispersant and a sterol or stanol ester made by reacting a sterol or a stanol and a carboxylic acid in the presence of an effective amount of a catalyst selected from the group consisting of calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide and combinations thereof.

2. The process of claim 1 wherein the sterol is .beta.-sitosterol.

4. The process of claim 1 wherein the catalyst is calcium hydroxide, calcium oxide or a calcium salt of a carboxylic acid.

5. The process of claim 1 wherein the carboxylic acid is a carboxylic acid having from about 2 to 22 carbon atoms.

6. A process which comprises reacting β-sitostanol with a carboxylic acid in the presence of an effective amount of calcium oxide.

7. The process of claim 6 wherein the carboxylic acid is a carboxylic acid having from about 2 to 22 carbon atoms.

8. The process of claim 1 wherein the carboxylic acid is a mixture of long chain carboxylic acids derived from sunflower oil, palm kernel oil, coconut oil, rape seed oil, tallow, corn oil, canola oil, linseed oil, palm oil, olive oil, sesame. . .
9. A process which comprises reacting .beta.-sitosterol with a carboxylic acid in the presence of an effective amount of calcium oxide.

10. The process of claim 1 wherein the antioxidant is vitamin C, vitamin E, β-carotene, an extract of the bark of the maritime pine, Pinus maritima, or combinations thereof.
. . .
11. A food additive composition comprising an edible solubilizing agent, an effective amount of a suitable antioxidant and an effective amount of a suitable dispersant and a sterol or stanol ester made by reacting a sterol or a stanol and a carboxylic acid in the presence of an effective amount of a catalyst selected from the group consisting of calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide and combinations thereof.

12. The composition of claim 11 wherein the sterol is .beta.-sitosterol.

14. The composition of claim 11 wherein the catalyst is calcium hydroxide, calcium oxide or a calcium salt of a carboxylic acid.

15. The composition of claim 11 wherein the carboxylic acid is a carboxylic acid having from about 2 to 22 carbon atoms.

16. The composition of claim 11 wherein the antioxidant is vitamin C, vitamin E, β-carotene, an extract of the bark of the maritime pine, Pinus maritima, or combinations thereof.
. . .
17. The composition of claim 11 wherein the carboxylic acid is a mixture of long chain carboxylic acids derived from sunflower oil, palm kernel oil, coconut oil, rape seed oil, tallow, corn oil, canola oil, linseed oil, palm oil, olive oil, sesame. . .
18. The composition of claim 17 wherein the mixture of long chain carboxylic acids derived from sunflower oil.

19. A process which comprises reacting .beta.-sitosterol with a carboxylic acid in the presence of an effective amount of calcium oxide.

20. The composition of claim 11 wherein the antioxidant is vitamin C, vitamin E, β-carotene, an extract of the bark of the maritime pine, Pinus maritima, or combinations thereof.

. . .

21. A food additive made by the process comprising combining an edible solubilizing agent, an effective amount of a suitable antioxidant, an effective amount of a suitable dispersant and a sterol or stanol ester made by reacting a sterol or a stanol and a carboxylic acid in the presence of an effective amount of a catalyst selected from the group consisting of calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide and combinations thereof.

22. The food additive of claim 21 wherein the sterol is .beta .-sitosterol.

24. The food additive of claim 21 wherein the catalyst is calcium hydroxide, calcium oxide or a calcium salt of a carboxylic acid.

25. The food additive of claim 21 wherein the carboxylic acid is a carboxylic acid having from about 2 to 22 carbon atoms.

26. The food additive of claim 21 wherein the carboxylic acid is a mixture of long chain carboxylic acids derived from sunflower oil, palm kernel oil, coconut oil, rape seed oil, tallow, corn oil, canola oil, linseed oil, palm oil, olive oil, sesame. . .

27. The food additive of claim 21 wherein the antioxidant is vitamin C, vitamin E, β-carotene, an extract of the bark of the maritime pine, Pinus maritima, or combinations thereof.

. . .

28. A composition comprising an edible solubilizing agent, an effective amount of a suitable antioxidant, an effective amount of a suitable dispersant and a compound of the formula I ##STR5## wherein R.sup.1 is an aliphatic or aromatic moiety having from one to. . .

38. A composition made by the process which comprises combining an edible solubilizing agent, an effective amount of a suitable antioxidant, an effective amount of a suitable dispersant and a compound of the formula I ##STR11## wherein R.sup.1 is an aliphatic or aromatic moiety having from one to. . . . of cholesterol into the bloodstream comprising orally introducing into the body an effective amount of a substance containing a β-sitostanol ester wherein the ester is made by reacting β-sitostanol and a carboxylic acid in the presence of an effective amount of a catalyst selected from the group consisting of calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide and combinations thereof.

49. The method of claim 48 wherein the substance containing a β-sitostanol ester is comprised of an additive comprised of from about 70% to about 80% sunflower oil, rape seed oil or a combination thereof; from about 1% to about 2% vitamin E, an extract of the bark. . . maritime pine, Pinus maritima or a combination thereof; and from about 10% to about 25% of a β-sitostanol fatty acid ester prepared by the method

according to the invention.

51. The process of claim 48 wherein the catalyst is calcium hydroxide, calcium oxide or a calcium salt of a carboxylic acid.

52. The process of claim 48 wherein the carboxylic acid is a carboxylic acid having from about 2 to 22 carbon atoms.

53. A process which comprises reacting a sterol, a stanol, or a combination thereof with a carboxylic acid in the presence of an effective amount of a catalyst selected from the group consisting of calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide and combinations thereof.

54. The process of claim 53 wherein said sterol is .beta.-sitosterol.

56. The process of claim 53 wherein said catalyst is calcium hydroxide, calcium oxide or a calcium salt of a carboxylic acid.

57. The process of claim 53 wherein said carboxylic acid is a carboxylic acid having from about 2 to 22 carbon atoms.

58. A process which comprises reacting β-sitostanol with a carboxylic acid in the presence of an effective amount of calcium oxide.

59. The process of claim 58 wherein said carboxylic acid is a carboxylic acid having from about 2 to 22 carbon atoms.

60. The process of claim 59 wherein said carboxylic acid is a mixture of long chain carboxylic acids derived from sunflower oil, palm kernel oil, coconut oil, rape seed oil, tallow, corn oil, canola oil, linseed oil, palm oil, olive oil, sesame. . .
. . the steps of: (1) forming a reaction mixture comprised of a sterol, a stanol, or a combination thereof with a carboxylic acid in the presence of an effective amount of a catalyst selected from the group consisting of calcium hydroxide, magnesium hydroxide and a combination in a reaction zone; (2) passing at least a portion of said reaction mixture through.
. .
63. The process of claim 61 wherein said catalyst is calcium oxide.

64. A process which comprises reacting a sterol, a stanol or a combination thereof with an carboxylic acid ester in the presence of an effective amount of a catalyst selected from the group consisting of calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide and combinations thereof.

65. The process of claim 64 wherein said sterol is .beta.-sitosterol.

67. The process of claim 64 wherein said catalyst is calcium

hydroxide, calcium oxide or a calcium salt of a carboxylic acid.

68. The process of claim 64 wherein said carboxylic acid is a carboxylic acid having from about 2 to 22 carbon atoms.

69. The process of claim 64 wherein said ester is a methyl ester of a C.sub.6-22 fatty acid or a triglyceride.

70. A process which comprises reacting β-sitostanol with a carboxylic acid ester in the presence of an effective amount of calcium oxide.

71. A process which comprises the steps of: (1) forming a reaction mixture comprised of a sterol, a stanol, or a combination thereof with a carboxylic acid ester in the presence of an effective amount of a catalyst selected from the group consisting of calcium hydroxide, magnesium hydroxide and a combination in a reaction zone; (2) passing at least a portion of said reaction mixture through. . . . . with a dicarboxylic acid in the presence of an effective amount of a catalyst selected from the group consisting of calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide and combinations thereof.

92. The compound of claim 83 wherein said catalyst is calcium oxide.

L14 ANSWER 3 OF 3 USPATFULL on STN

ACCESSION NUMBER:	2002:121365 USPATFULL
TITLE:	Sterol esters as food additives
INVENTOR(S):	Milstein, Norman, Montgomery, OH, United States Biermann, Manfred, Cincinnatti, OH, United States Leidl, Peter, Illertissen, GERMANY, FEDERAL REPUBLIC OF von Kries, Rainer, Illertissen, GERMANY, FEDERAL REPUBLIC OF
PATENT ASSIGNEE(S):	Cognis Corporation, Gulph Mills, PA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6394230	B1	20020528
APPLICATION INFO.:	US 1998-83584		19980521 (9)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1998-72434, filed on 4 May 1998, now abandoned		

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-69790P	19971216 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	GRANTED
PRIMARY EXAMINER:	Qazi, Sabiha
LEGAL REPRESENTATIVE:	Drach, John E., Ettelman, Aaron R.
NUMBER OF CLAIMS:	20
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	0 Drawing Figure(s); 0 Drawing Page(s)
LINE COUNT:	543

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A food additive useful for lowering serum cholesterol in humans contains a sterol or stanol ester of a fatty acid or a dicarboxylic acid ester of a sterol or stanol made by reacting a sterol,

stanol and a carboxylic acid in the presence of an effective amount of a catalyst selected from the group consisting of calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide and combinations thereof described herein below.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Sterol esters as food additives

AB A food additive useful for lowering serum cholesterol in humans contains a sterol or stanol ester of a fatty acid or a dicarboxylic acid ester of a sterol or stanol made by reacting a sterol, stanol and a carboxylic acid in the presence of an effective amount of a catalyst selected from the group consisting of calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide and combinations thereof described herein below.

SUMM . . . relationship to cholesterol but differ in the configuration of the side chains at the 17-position. It is well known that .beta .-sitosterol and the fatty acid esters of .beta.-sitosterol are effective in reducing serum cholesterol. Recent studies have found that β-sitostanol and the fatty acid esters of β-sitostanol are particularly effective in reducing serum cholesterol and LDL levels. It has been recently reported that the fatty acid esters of β-sitostanol are particularly effective cholesterol-reducing agents presumably because they are in solution. Such esters can be introduced into the body as additives in food products such as margarine. Margarines containing .beta.-sitosterol and those containing .beta.-sitosterol fatty acid esters as well as margarines containing β-sitostanol and β-sitostanol fatty acid esters have been shown to reduce serum cholesterol levels in humans.

SUMM The present invention pertains to a food additive containing a sterol or stanol ester of a fatty acid or a dicarboxylic acid ester of a sterol or stanol made by the process described herein below. The food additive can be incorporated into food. . . . absorption of cholesterol from foods and/or beverages. The food additive is prepared by combining a sterol and/or stanol fatty acid ester thereof and/or a dicarboxylic acid ester of a sterol or stanol made by the process described herein and an edible solubilizing agent, an effective amount of a suitable antioxidant and an effective amount of a suitable dispersant. The sterol and/or stanol esters made by the process described herein can be used without removing the catalyst because the catalyst is non-toxic and used at low levels. Another advantage is that when the fatty acid esters of sterols or stanols are prepared by transesterification, the ester that is transesterified can be either a lower alkyl ester such as a methyl or an ethyl ester or a triglyceride which is a triglyceryl ester of a C.sub.6-22 fatty acid such as a conventional fat or oil.

SUMM . . . cholesterol into the bloodstream which comprises orally introducing into the body an effective amount of a substance containing a β-sitostanol ester made by reacting a stanol and a carboxylic acid in the presence of an effective amount of a catalyst selected from the group consisting of calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide and combinations thereof.

SUMM The food additive according to the invention is comprised of a sterol and/or stanol ester of a fatty acid wherein the ester is made by reacting a sterol and/or stanol with a fatty acid having from 6 to 22 carbon atoms in the presence of an effective amount of a

catalyst selected from the group consisting of calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide and combinations thereof or a dicarboxylic acid ester of a sterol or stanol of the formula I. Since the catalyst is non-toxic and used at low levels, the sterol and/or stanol ester of the fatty acid can be added directly to foods without further processing such as removal of the catalyst. The. . . suitable sterols include, but are not limited to, campesterol, ergosterol, stigmasterol, sitosterol or a combination thereof. A preferred sterol is .beta .-sitosterol. A commercially available combination of sterols is GENEROL® 122N sterols as set forth herein. The stanol can be any stanol.. . .

SUMM The amount of sterol and/or stanol fatty acid ester that can be used in the food additive is an effective amount which is any amount necessary to either reduce. . . from foods and/or beverages. A preferred food additive composition of the instant invention comprises from about 70% to about 80% vegetable oil, from about 1% to about 2% tocopherols, and from about 10% to about 25% sterol and/or stanol fatty acid ester prepared by the method according to the invention.

SUMM The food additive is prepared by combining a sterol and/or stanol ester of a fatty acid made by the process described herein and an edible solubilizing agent, an effective amount of a suitable antioxidant and an effective amount of a suitable dispersant. The solubilizing agent can be vegetable oil such as, for example, sunflower oil, palm kernel oil, coconut oil, rape seed oil, tallow, corn oil, canola oil, linseed oil, palm oil, olive oil, sesame oil, safflower oil, and the like, monoglycerides, diglycerides, triglycercides, tocopherols, and the like, and mixtures thereof. The antioxidant can be ascorbic acid (Vitamin C), tocopherols such as α- tocopherol (vitamin E), β-carotene, an extract of the bark of the maritime pine, Pinus maritima and combinations thereof. The extract of. . . precipitate which may be purified by repeating the dissolution in ethyl acetate and precipitation with chloroform. Mixtures of the above antioxidants can also be used.

SUMM A suitable dispersant is any biologically acceptable surface active agent, examples of which include, but are not limited to, an alkyl polyglycoside, lecithin, polysorbate 80, sodium lauryl sulfate, and the like. The alkyl polyglycosides which can be used in the invention have the formula V

SUMM . . . a value from 0 to about 12; a is a number having a value from 1 to about 6. Preferred alkyl polyglycosides which can be used in the compositions according to the invention have the formula I wherein Z is a glucose residue and b is zero. Such alkyl polyglycosides are commercially available, for example, as APG®, GLUCOPON®, PLANTAREN® or AGRIMUL® surfactants from Henkel Corporation, Ambler, Pa. 19002. Examples of. . .

SUMM 1. GLUCOPON® 220 Surfactant--an alkyl polyglycoside in which the alkyl group contains 8 to 10 carbon atoms and having an average degree of polymerization of 1.5.

SUMM 2. GLUCOPON® 225 Surfactant--an alkyl polyglycoside in which the alkyl group contains 8 to 10 carbon atoms and having an average degree of polymerization of 1.7.

SUMM 3. GLUCOPON® 600 Surfactant--an alkyl polyglycoside in which the alkyl group contains 12 to 16 carbon atoms and having an average degree of polymerization of 1.4.

SUMM 4. GLUCOPON® 625 Surfactant--an alkyl polyglycoside in which the alkyl group contains 12 to 16 carbon atoms and having an average degree of polymerization of 1.4.

SUMM 5. APG® 325 Surfactant--an alkyl polyglycoside in which the alkyl group contains 9 to 11 carbon atoms and having an

average degree of polymerization of 1.6.

SUMM 6. PLANTAREN® 2000 Surfactant--an alkyl polyglycoside in which the alkyl group contains 8 to 16 carbon atoms and having an average degree of polymerization of 1.4.

SUMM 7. PLANTAREN® 1300 Surfactant--an alkyl polyglycoside in which the alkyl group contains 12 to 16 carbon atoms and having an average degree of polymerization of 1.6.

SUMM 8. AGRIMUL® PG 2067 Surfactant--an alkyl polyglycoside in which the alkyl group contains 8 to 10 carbon atoms and having an average degree of polymerization of 1.7.

SUMM Other examples include alkyl polyglycoside surfactant compositions which are comprised of mixtures of compounds of formula I as described in U.S. Pat. Nos. 5,266,690 and. . .

SUMM . . . Products (1985), the entire contents of which are incorporated herein by reference. The amount of sterol and/or stanol fatty acid ester useful in the novel food additive is an effective amount which is any amount necessary to either reduce serum cholesterol. . . from foods and/or beverages. A preferred food additive composition of the instant invention comprises from about 70% to about 80% vegetable oil, from about 1% to about 2% tocopherols, and from about 10% to about 25% sterol and/or stanol fatty acid ester prepared by the method according to the invention. Particularly preferred compositions are composed of from about 70% to about 80% sunflower oil and/or rape seed oil, from about 1% to about 2% vitamin E and/or an extract of the bark of the maritime pine, Pinus maritima and from about 10% to about 25% of a sterol and/or stanol fatty acid ester prepared by the method according to the invention.

SUMM . . . cholesterol into the bloodstream which comprises orally introducing into the body an effective amount of a substance containing a β-sitostanol ester made by reacting β-sitostanol and a carboxylic acid in the presence of an effective amount of a catalyst selected from the group consisting of calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide and combinations thereof. The cholesterol-lowering ability of fatty acid esters of β-sitostanol is described in U.S. Pat. No. 5,502,045, the entire contents of which are incorporated herein by reference. The fatty acid esters of β-sitostanol made by the process described herein can be orally introduced by ingesting food products containing the food additives. . . cooking oils or shortening containing a food additive according to the invention. A particularly effective amount of β-sitostanol fatty acid esters is from about 0.2 to about 20 grams per day. Particularly preferred additives are composed of from about 70% to about 80% sunflower oil and/or rape seed oil, from about 1% to about 2% vitamin E and/or an extract of the bark of the maritime pine, Pinus maritima and from about 10% to about 25% of a β-sitostanol fatty acid ester prepared by the method according to the invention.

SUMM In regard to the esterification process used to make the sterol and/or stanol esters which can be used in the novel food additive, any aliphatic, cycloaliphatic, or aromatic mono- or poly-carboxylic acid having at least 2 carbon atoms or mixtures of such acids can be used in the process according to the invention. Examples of aliphatic mono-carboxylic acids include, but are not limited to acetic, propionic, valeric, pelargonic, palmitic, lauric, oleic, linoleic acid, and the like. Examples of cycloaliphatic mono-carboxylic acids include, but are not limited to cyclopentane carboxylic acid, cyclohexane carboxylic acid, cyclohexene carboxylic acid and the like. Examples of aromatic mono-carboxylic acids include, but are not limited to benzoic acid, toluic acid, aminobenzoic acid and the like. Examples

of aliphatic poly-carboxylic acids include, but are not limited to oxalic, malonic, adipic, azelaic acid, C-36 dimer acid, citric acid and the like. Examples of aromatic poly-carboxylic acids include, but are not limited to phthalic acid, trimellitic acid and the like. Preferred carboxylic acids are mixtures of long chain carboxylic acids such as those derived from naturally occurring oils such as sunflower oil, palm kernel oil, coconut oil, rape seed oil, tallow, corn oil, canola oil, linseed oil, palm oil, olive oil, sesame. . . Fat Products, the entire contents of which are incorporated herein by reference. Preferred fatty acid mixtures are those obtained from sunflower oil and rape seed oil.

SUMM The direct or transesterification modifications of the esterification processes can be carried out in the presence of a calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide catalyst or a combination of such catalysts. One advantage of the method according to the invention is that. . . removed by contacting the reaction product with a chelating agent such as L-tartaric acid or EDTA. The preferred catalysts are calcium hydroxide, calcium oxide and the calcium salt of a fatty acid having from about 10 to about 22 carbon atoms. Calcium oxide is a particularly preferred catalyst. The amount that can be used is an effective amount which is any amount required to effect the conversion of a sterol or stanol to the corresponding ester. Typically, the amount will range from about 0.01% to 0.2% based on the total weight of the reaction mixture and. . .

SUMM The transesterification process according to the invention can be carried out using any type of carboxylic acid ester. Such esters include simple esters such as lower alkyl esters which include, for example, methyl, ethyl, propyl, or butyl esters or higher alkyl esters such as pentyl, hexyl, heptyl and the like or triglycerides which are triglyceryl esters of C.sub.6-22 fatty acids such as conventional fats or oils. The transesterification conditions will vary according to the type of ester employed. If a glyceride is used, the temperature will be in the range of from about 210° C. to about 250° C., preferably from about 220° C. to about 230° C. If an ester of a lower molecular weight alcohol is used such as a methyl or ethyl ester such that the alcohol formed will be readily removed under the reaction conditions as, opposed to the use of a. . .

SUMM . . . commercial scale is that since no low molecular weight alcohol is produced as in, for example, transesterification of a methyl ester, there is no foaming in a reactor due to the evolution of the low molecular weight alcohol such as methanol.. . .

SUMM The process according to the invention is particularly useful for the preparation of dicarboxylic acid esters of sterols and/or stanols wherein the dicarboxylic acids are fully esterified or partially esterified. Such compounds have the formula I. . . .

SUMM . . . be hydrogen. In the instances where only one of R.sup.2 or R.sup.3 is hydrogen refer to the partial or half esters of the dicarboxylic acids. These compounds are useful as for reducing serum cholesterol and LDL levels. Preferred compounds of the. . .

SUMM Most preferred compounds of the formula I include the disitostanol ester of azelaic acid, the disitostanol ester of brassylic acid, the disitostanol ester of decanedioic acid, the disitostanol ester of dodecanedioic acid, the disitosterol ester of azelaic acid, the disitosterol ester of brassylic acid, the disitostanol ester of decanedioic acid and, the disitosterol ester of dodecanedioic acid, the sitostanol monoester of azelaic acid, the sitostanol monoester of brassylic acid, the sitostanol monoester of decanedioic. . .

DETD . . . agitating with a nitrogen sparge. This required about one half hour. After the addition of the stanol, 0.34 grams of calcium hydroxide was added and the pressure was gradually decreased to 27 inches, while the temperature was increased to 230° C. After. . .

DETD . . . agitating with a nitrogen sparge. This required about one half hour. After the addition of the stanol, 0.34 grams of calcium oxide was added and the pressure was gradually decreased to 27 inches, while the temperature was increased to 210° C. After. .

DETD A dicarboxylic ester is made by reacting one mole of a sterol or stanol with a 1/2 mole of a dicarboxylic acid in the presence of calcium oxide at 210 degrees under reduced pressure according to the procedure of Examples 1 and 2 above.

DETD . . . with a nitrogen sparge. This required about one half hour. After the addition of the GENEROL® 122N, 0.34 grams of calcium oxide was added and the pressure was gradually decreased to 30 mbar while the temperature was increased to 210° C. After. . .

CLM What is claimed is:

. . . the group consisting of sterols, stanols, and combinations thereof with at least one member selected from the group consisting of carboxylic acids and carboxylic acid esters in the presence of a catalytically effective amount of a catalyst selected from the group consisting of calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide and combinations thereof, wherein said reaction mixture includes at least a portion of said catalyst.

2. The food additive of claim 1 wherein said sterol comprises . beta.-sitosterol.

4. The food additive of claim 1 wherein said catalyst consists essentially of at least one member selected from the group consisting of calcium hydroxide, calcium oxide or a calcium salt of a carboxylic acid.

5. The food additive of claim 1 wherein said carboxylic acid or carboxylic acid ester comprises a carboxylic acid or carboxylic acid residue having from about 2 to 22 carbon atoms.

6. The food additive of claim 1, wherein said reaction mixture is formed by reacting β-sitostanol with a carboxylic acid or carboxylic acid ester in the presence of a catalytically effective amount of calcium oxide .

7. The food additive of claim 6 wherein said carboxylic acid or carboxylic acid ester comprises a carboxylic acid or carboxylic acid residue having from about 2 to 22 carbon atoms.

8. The food additive of claim 7 wherein said carboxylic acid comprises a mixture of long chain carboxylic acids obtained from at least one member selected from the group consisting of sunflower oil, palm kernel oil, coconut oil, rape seed oil, tallow, corn oil, canola oil, linseed oil, palm oil, olive oil, sesame. . .

11. The food additive of claim 9 wherein said catalyst comprises calcium oxide.

12. The food additive of claim 1, wherein said reaction mixture is formed by reacting at least one member selected from the group consisting of sterols, stanols, and combinations thereof with a carboxylic acid ester in the presence of a catalytically effective amount of a catalyst selected from the group consisting of calcium oxide, calcium hydroxide, a calcium salt of a carboxylic acid, magnesium hydroxide and combinations thereof.

13. The food additive of claim 12 wherein said sterol comprises . beta.-sitosterol.

15. The food additive of claim 12 wherein said catalyst consists essentially of at least one member selected from the group consisting of calcium hydroxide, calcium oxide or a calcium salt of a carboxylic acid.

16. The food additive of claim 12 wherein said carboxylic acid of the ester is a carboxylic acid having from about 2 to 22 carbon atoms.

17. The food additive of claim 12 wherein said ester comprises a methyl ester of a C.sub.6-22 fatty acid or a triglyceride of a C.sub.6-22 fatty acid.

18. The food additive of claim 12, wherein said reaction mixture is formed by reacting β-sitostanol with a carboxylic acid ester in the presence of an effective amount of calcium oxide.